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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/044,442	01/11/2002	Malcolm Whitman	WHIT-06919	9317

7590 01/11/2005

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/044,442	WHITMAN ET AL.	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4,7,8,11,12,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4,7,8,11,12,15,16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 3, 4, 7, 8, 11, 12, 15, 16 are pending.

Applicant's election without traverse of group II in the reply filed on 11/01/2004 is acknowledged.

Priority

The benefit claim in the preliminary amendment filed 01/11/2002 does not comply with the relevant statute and patent regulations. Specifically, the benefit claim "This is a divisional of copending application(s) U.S. Serial No. 60/047,911" does not comply with the relevant statute and patent regulations because the present application was not filed within twelve months of the filing date of the provisional application. A proper benefit claim in this situation would be "This application is a divisional of U. S. Application No. 09/087,134, filed 05/28/1998, now U. S. Patent No. 6,365,711, which claims the benefit of 60/047,991, filed 05/28/1997."

If a relationship between a nonprovisional application and a prior provisional application is submitted it may be unclear whether applicant wishes to claim the domestic benefit of the provisional application under 35 U.S.C. 119(e), or the benefit of an earlier application's filing date under 35 U.S.C. 120. Thus, applicants seeking to claim the domestic benefit of a provisional application under 35 U.S.C. 119(e) should not state that the application is a "divisional" of a provisional application, nor should it be stated that the application claims benefit under 35 U.S.C. 120 of a provisional application. If such a claim is submitted in an application transmitted to the Office other than through the

Electronic Filing System, it will be entered into the Office computer system as a claim to the "benefit" of the provisional application. Although 35 U.S.C. 120 does not preclude a benefit claim to a provisional application (that is, one could obtain the benefit under 35 U.S.C. 120 of a prior filed provisional application), such a benefit claim under 35 U.S.C. 120 is not recommended as such a claim may have the effect of reducing the patent term, as the term of a patent issuing from such an application may be measured from the filing date of the provisional application pursuant to 35 U.S.C. 154(a)(2). Instead, applicants should state "This application claims the benefit of U.S. Provisional Application No. 60/ - , filed - ", or "This application claims the benefit of U.S. Provisional Application No. 60/ - , filed - , and U.S. Provisional Application 60/ - , filed - ."

Applicants are advised that the Office will not recognize any benefit claim where there is no indication of the relationship between the nonprovisional applications, or no indication of the intermediate nonprovisional application that is directly claiming the benefit of a provisional application. Applicants are also reminded that, even if the Office has recognized a benefit claim that includes the proper reference by entering it into the Office's database and including it on applicant's filing receipt, the benefit claim is not a proper benefit claim under 35 U.S.C. 119(e) and/or 35 U.S.C. 120, and 37 CFR 1.78, unless the reference is included in an application data sheet, or the first sentence of the specification, and all other requirements are met.

Applicants are also reminded that, if an amendment to the specification, or an application data sheet (ADS), is submitted in an application under final rejection, the amendment or ADS must be in compliance with 37 CFR 1.116. The amendment or ADS filed in an application under final rejection will not be entered as a matter of right. See

MPEP 714.12 and 714.13. Therefore, applicants should consider filing a request for continued examination (RCE) (including fee and submission) under 37 CFR 1.114 with the petition to accept an unintentionally delayed benefit claim, the surcharge, and an amendment that adds the proper reference to the first sentence of the specification or an ADS.

The Office requires a petition and the surcharge to correct the claim. See Requirements for Claiming the Benefit of Prior-Filed Applications Under Eighteen-Month Publication Provisions, 66 Fed. Reg. 67087, 67089-90 (Dec. 28, 2001).

Appropriate correction is required.

Specification

The application is not fully in compliance with the sequence rules, 37 C.F.R. § 1.821-1.825. Specifically, the specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed. See Figure 10. This is not meant to be an exhaustive list of places where the specification fails to comply with the sequence rules. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification. The application cannot issue until it is in compliance. Nucleic acid sequences with 10 or more nucleotides, at least 4 of which are specifically defined, must comply with the sequence rules. Amino acid sequences with 4 or more residues, at least 4 of which are specifically defined, must comply with the sequence rules. Sequence identifiers can also be used to discuss and/or claim parts or fragments of a properly presented sequence. For

example, language such as "residues 14 to 243 of SEQ ID NO:23" is permissible and the fragment need not be separately presented in the "Sequence Listing." Applicant may bring the figure(s) into compliance by amending either the figure(s) or the "Brief Description of the Drawings" to recite the appropriate sequence identifier.

Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 4, 7, 8, 11, 12, 15, 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to or encompass a "fusion protein comprising a polypeptide fragment of Smad3" and a "fusion protein comprising a polypeptide fragment of FAST-1." The following passages from the specification seem most relevant for construing "fusion protein comprising a polypeptide fragment of Smad3" and "fusion protein comprising a polypeptide fragment of FAST-1":

Page 9, full paragraph 3:

the invention features substantially pure polypeptides or fragments thereof having about 50% or greater amino acid sequence identity, about 75% or greater amino acid sequence identity, and about 90% or greater amino acid sequence identity to the comparable amino acid sequence of the mammalian FAST-1 protein or polypeptide fragment thereof. Preferably, the identity is determined by comparison with the FAST-1 SID (i.e., FAST-1 amino acids 380 to 509 of Xenopus FAST-1, amino acids 234 to 365 of human FAST-1, or amino acids 309 to 398 of mouse FAST-1). In another preferred embodiment, the polypeptide fragment binds to Smad2 or Smad3.

Page 11, full paragraph 2:
"Protein" or "polypeptide" or "polypeptide fragment" means any chain of more than two amino acids, regardless of post-translational modification (e.g., glycosylation or phosphorylation), constituting all or part of a naturally-occurring polypeptide or peptide, or constituting a non-naturally occurring polypeptide or peptide.

Page 12, full paragraph 1:
"Smad3 protein or polypeptide fragment thereof" means a Smad3 protein (or polypeptide fragment or domain thereof) found in Xenopus or mammalian (e.g. mouse or human) cells. A preferred domain of Smad3 is the Mad Homology 2 (MH2) domain (i.e., amino acids 253 to 446 of human Smad3). Also preferred are polypeptide fragments comprising the MH2 domain, that consist of, at maximum, human Smad3 amino acids 230 to 446, and subfragments thereof, consisting of, at maximum, amino acids 253 to 446, amino acids 253 to 424, or amino acids 230 to 424, or the corresponding amino acids that comprise Smad3 MH2 domains from other species. These polypeptide fragments are capable of interacting with the FAST-1 SID domain.

Page 12, full paragraph 2:
"Mammalian FAST-1 protein or polypeptide fragment thereof" means an amino acid sequence derived from a mammalian cell which displays at least 30%, preferably, 40%, more preferably 50%, still more preferably 60%, 70%, or even 80% means amino acid sequence identity to a FAST-1 Smad Interaction Domain (SID), i.e., amino acids 380 to 506 of the Xenopus FAST-1 protein, amino acids 234to 365 of the human FAST-1 -protein, or amino acids 309 to 398 of tie mouse FAST-1 protein. The length of comparison, generally will be at least 16 amino acids, preferably at least 20 amino acids, more preferably at least 25 amino acids, and most preferably at least 30 amino acids. Preferably, a mammalian FAST-1 protein, or polypeptide fragment thereof, is able to bind Smad2. The FAST-1 SID is a preferred polypeptide fragment of FAST-1.

Accordingly, the claims are directed to or encompass a genus of fusion proteins comprising a single amino acid of Smad3 and a genus of fusion proteins comprising a single amino acid of FAST-1. The specification and claim do not limit the distinguishing attributes shared by members of the genera. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to a Smad3 or FAST-1 polypeptide. Thus, the scope of the claim includes numerous structural variants, and the genera are highly variant because a significant number of structural differences between genus members is permitted. Features that could distinguish compounds in the genera from others in the protein class are missing from the disclosure. Essentially no common structural attributes identify the members of the genera. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure essentially fails to limit the common attributes or characteristics that identify members of the genera, and because the genera are highly variant, the specifically exemplified vertebrate proteins alone are insufficient to describe the genera in the present claims. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the genera in the present claims.

Claims 3, 4, 7, 8, 11, 12, 15, 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening for compounds that disrupt the interaction of a fragment of a vertebrate FAST-1 with a vertebrate Smad3, wherein said fragment of FAST-1 binds said fragment of Smad3, does not reasonably

provide enablement for the claimed screening method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to or encompass a screening method comprising a reporter gene assay. The reporter gene assay comprises a reporter gene construct comprising a reporter gene operably linked to a DNA-binding protein recognition site, a first fusion protein comprising a polypeptide fragment of Smad3 and a moiety that binds the DNA-binding protein recognition site in the reporter gene construct, a second fusion protein comprising a polypeptide fragment of FAST-1 and a gene activating moiety, a test compound, and measuring reporter gene expression.

However, the claims do not require that the fragment of Smad3 interact with the fragment of FAST-1 and thus recruit the Smad3/FAST-1 complex to the reporter DNA or a site operably linked to the reporter gene, such that reporter gene transcription is stimulated. Furthermore, there are no working examples of transcriptional response to Smad3 and FAST-1 fragments. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. Lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art.

The claims do not require that the "gene activating moiety" activate reporter gene expression in the reporter gene assay. There is nothing in the present disclosure regarding a universal gene activating moiety that will activate any and/or all genes. The claims do not require that the reporter gene be operably linked with a site to which the

"gene activating moiety" binds or activates transcription. The present specification provides no guidance for, or working examples of, a "gene activating moiety." While a specification need not disclose what is well known in the art, that rule does not excuse an applicant from providing a complete disclosure. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Modulating TGF-β superfamily signaling encompasses activating and repressing reporter gene transcription. However, the claims do not require comparing reporter gene expression in the presence and absence of the test compound. The claims do not require that the reporter gene be expressed in the absence of the test compound. In the absence of reporter gene expression it would be impossible to ascertain if the test compound is a repressor of TGF-β superfamily signaling. The claims do not require that the fragment of Smad3 interact with the fragment of FAST-1. In the absence of an interaction it would be impossible to ascertain if the test compound is a repressor of TGF-β superfamily signaling.

The following passages from the specification seem most relevant for construing "fusion protein comprising a polypeptide fragment of Smad3" and "fusion protein comprising a polypeptide fragment of FAST-1":

> Page 9, full paragraph 3:
> the invention features substantially pure polypeptides or fragments thereof having about 50% or greater amino acid sequence identity, about 75% or greater amino acid sequence identity, and about 90% or greater amino acid sequence identity to the comparable amino acid sequence of the mammalian FAST-1 protein or polypeptide fragment thereof. Preferably, the identity is determined by comparison with the FAST-1 SID (i.e., FAST-1 amino acids 380 to 509 of Xenopus FAST-1, amino acids 234 to 365 of human FAST-1, or amino acids 309

to 398 of mouse FAST-1). In another preferred embodiment, the polypeptide fragment binds to Smad2 or Smad3.

Page 11, full paragraph 2:
"Protein" or "polypeptide" or "polypeptide fragment" means any chain of more than two amino acids, regardless of post-translational modification (e.g., glycosylation or phosphorylation), constituting all or part of a naturally-occurring polypeptide or peptide, or constituting a non-naturally occurring polypeptide or peptide.

Page 12, full paragraph 1:
"Smad3 protein or polypeptide fragment thereof" means a Smad3 protein (or polypeptide fragment or domain thereof) found in Xenopus or mammalian (e.g. mouse or human) cells. A preferred domain of Smad3 is the Mad Homology 2 (MH2) domain (i.e., amino acids 253 to 446 of human Smad3). Also preferred are polypeptide fragments comprising the MH2 domain, that consist of, at maximum, human Smad3 amino acids 230 to 446, and subfragments thereof, consisting of, at maximum, amino acids 253 to 446, amino acids 253 to 424, or amino acids 230 to 424, or the corresponding amino acids that comprise Smad3 MH2 domains from other species. These polypeptide fragments are capable of interacting with the FAST-1 SID domain.

Page 12, full paragraph 2:
"Mammalian FAST-1 protein or polypeptide fragment thereof" means an amino acid sequence derived from a mammalian cell which displays at least 30%, preferably, 40%, more preferably 50%, still more preferably 60%, 70%, or even 80% means amino acid sequence identity to a FAST-1 Smad Interaction Domain (SID), i.e., amino acids 380 to 506 of the Xenopus FAST-1 protein, amino acids 234to 365 of the human FAST-1 -protein, or amino acids 309 to 398 of tie mouse FAST-1 protein. The length of comparison, generally will be at least 16 amino acids, preferably at least 20 amino acids, more preferably at least 25 amino acids, and most preferably at least 30 amino acids. Preferably, a mammalian FAST-1 protein, or polypeptide fragment thereof, is able to bind Smad2. The FAST-1 SID is a preferred polypeptide fragment of FAST-1.

Accordingly, the claims are directed to or encompass a genus of fusion proteins comprising a single amino acid of Smad3 and a genus of fusion proteins comprising a single amino acid of FAST-1. Although inventors should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his

teachings, since such improvements, while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues in vertebrate FAST-1 and Smad3 polypeptides which are required for the functional and structural integrity of these proteins. It is this additional characterization of those disclosed, naturally occurring vertebrate polypeptides that is required in order to obtain the functional and structural data needed to permit one to produce FAST-1 and Smad3 polypeptide fragments which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides

sufficient guidance to permit one to identify those embodiments which are more likely to work than not without actually making and testing them then the instant application does not support the breadth of the claims. In the instant case it is highly improbable that any protein having comprising a single amino acid of either FAST-1 or Smad3.

In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, the unpredictability in the art and the quantity of experimentation needed to make or use the invention based on the content of the disclosure, it would require undue experimentation for the skilled artisan to make and/or use the full scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 4, 7, 8, 15, 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 4, 7, 8, 15, 16 are indefinite because they recite the term "gene activating moiety." Because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "gene activating moiety" an artisan cannot determine what additional or material limitations are placed upon a claim by the presence of this element. The metes and bounds are not clearly set forth.

Double Patenting

Applicant is advised that should claim 11 be found allowable, claim12 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (571) 273-0890.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

David Romeo

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
JANUARY 9, 2005